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Previous lung disease and lung cancer risk among women (United States)

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Abstract

Objective: The association between previous lung diseases (PLD) and lung cancer risk has not been studied extensively. We conducted a registry-based case–control study to examine the relation between previous lung diseases and lung cancer among women in Missouri.
Methods: Incident cases (n = 676) were identified through the Missouri Cancer Registry for the period 1 January 1993 to 31 January 1994. Controls (n = 700) were selected through drivers' license files and Medicare files.
Results: Whether analyzing all respondents or in-person interviews only, elevated effect estimates were noted for several types of PLD. Elevated relative risk estimates were shown for chronic bronchitis (odds ratio [OR] = 1.7; 95% confidence interval [CI] = 1.2–2.3), emphysema (OR = 2.7; 95% CI = 1.8–4.2), pneumonia (OR = 1.6; 95% CI = 1.2–2.0), and for all PLDs combined (OR = 1.5; 95% CI = 1.2–1.9). Analysis of only direct interviews did not show a substantial or consistent pattern of change in relative risk estimates. Because PLDs identified close to the time of cancer diagnosis could conceivably be misdiagnosed, resulting from early lung cancer symptoms, we evaluated the effects on risk estimates of a ''latency exclusion'' of up to three years. When these exclusions were taken into account, ORs remained statistically significantly elevated only for emphysema.
Conclusion: When earlier epidemiologic findings and underlying biological and genetic factors are taken into account, an association between PLD and lung cancer is plausible.

Introduction

Mortality rates for lung cancer among US women increased 550% from 1950 to 1991 [1]. It is well accepted that cigarette smoking is responsible for the vast majority of lung cancers among women, with an attributable risk of approximately 80% [2]. The remaining risk factors for lung cancer among women are not nearly as well quantified. For example, it is believed that a composite of factors including exposure to environmental tobacco smoke, residential radon, occupational exposures, low vegetable consumption, and certain cooking practices (*e.g.* inhalation of rapeseed oil vapor) all contribute to lung cancer occurrence in women [3]. In addition, several population-based studies have examined the relationship between previous lung diseases (PLD) and lung cancer risk in nonsmokers and smokers [4–10]. The group of lung diseases that has been studied includes asthma, chronic bronchitis, pleurisy, pneumonia, and tuberculosis. Effect estimates from major studies have generally ranged from 1.2 to 2.0 for individual lung diseases and for a history of any PLD [3]. A recent European review of lung cancer risks concluded that PLD is a known, key risk factor for lung cancer [11].

This study was designed to add to the body of knowledge regarding PLD and lung cancer risk in women based on a population-based case–control study from Missouri. It also allowed us to examine the effects of proxy interviews and latency exclusions on effect estimates.

Subjects and methods

Cases

Cases were identified through the Missouri Cancer Registry, which is maintained by the Missouri Department of Health. The Registry began collecting data on incident cancer cases from public and private hospitals in 1972, and hospital reporting was mandated by law in 1984.

Registry reporting procedures have been discussed in more detail elsewhere [12]. To ensure complete reporting of female lung cancer cases for the current study, Registry staff completed special case ascertainment visits to participating hospitals, covering more than 95% of all lung cancer cases estimated for Missouri. The case series included Missouri women, aged 30–84 years, who were diagnosed with primary lung cancer between 1 January 1993 and 31 January 1994. Of the 783 women identified, 41 were not eligible either because they were not Missouri residents (n = 7) or did not have lung cancer (n = 34). Of the 742 eligible cases, 697 women or a proxy completed a telephone interview. Reasons for nonresponse include subject refusal (n = 13), physician refusal (n = 13), or the absence of a proxy respondent (n = 19).

Histologic confirmation of cases

In addition to the Registry-reported diagnosis of lung cancer case status, tissue slides were reviewed for histologic verification for 73.5% (n = 512) of the cases. Tissue slides were not available for remaining cases. Slides for these cases were examined simultaneously by three pathologists using a multi-headed microscope without knowledge of the referring pathologist's diagnosis. In surgical specimens, consensus diagnoses were obtained with the criteria outlined in the World Health Organization classification scheme [13]. When only cytologic material was available, consensus was obtained with standard cytologic criteria [14].

Controls

A population-based sample of controls was ascertained by two methods. For women under age 65, a random sample of state drivers' license files was provided by the Missouri Department of Revenue, with estimated coverage of over 90%. Among women aged 65–84 years, controls were generated from the Health Care Finance Administration's roster of Medicare recipients, which includes an estimated 95% of women in this age group [15].

As described in earlier publications [16–18], we used a two-stage randomized recruitment strategy to avoid the expected imbalance in smoking status among cases and controls [19]. The first stage involved a screening interview to obtain information on selected covariates and disease. In the second phase, we collected data from subjects with prespecified sampling probabilities in order to over-represent vulnerable individuals (*i.e.* smokers) to the same extent that they would be over-represented in the case series. Potential controls were also frequency-matched to cases using 5-year age strata. All controls were interviewed directly. Of the 3386 controls who were found eligible by screening criteria, 730 women were targeted for interview. Since the majority of the 3386 controls were nonsmokers, only a fraction of these were needed in the final control group. Therefore, a random sample of eligible controls were targeted for full interview – a total of 730 controls were targeted. From these, 700 women completed the telephone interview.

Questionnaire design and administration

Telephone interviews were conducted by trained interviewers. The first phase of the interview consisted of a telephone screening questionnaire to verify the age, race, and smoking status of cases and controls. For cases, the average time elapsed between lung cancer diagnosis and interview was 98 days. Among subjects who screened eligible and agreed to the full interview, the telephone-administered questionnaire consisted of sections on residential history, personal health history (including questions on 13 specific PLDs), reproductive history, occupation, and income. Questions on PLDs were as follows: (1) "Did a doctor ever tell you that you had: pneumonia, chronic bronchitis, emphysema, asthma, pleurisy, tuberculosis, abscess of the lung, COPD, asbestosis, silicosis, black lung, pneumoconiosis, farmer's lung, any other lung disease?"; (2) "How old were you when a doctor diagnosed this disease?"; and (3) "What year and month did a doctor diagnose this disease?". Following the telephone interview, a second questionnaire on dietary factors was provided to each subject when study staff visited each home to place radon detectors for another phase of the study [17]. At this time staff assisted each respondent with the completion of the diet questionnaire [18].

Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multiple logistic regression [20]. We initially examined numerous potential confounding

factors, including age, smoking history, dietary factors, and residential radon exposure. Results presented are adjusted for smoking history, since it was the only risk factor that attenuated the PLD-related effect estimates by 10% or more [21].

Results

Sociodemographic and smoking-related characteristics of cases and controls have been presented in detail elsewhere [16, 17]. Data shown in the tables represent subjects for whom complete data on PLD were available (676 cases and 700 controls). In brief, the average ages of cases and controls were 66.2 years and 66.4 years, respectively (Table 1). Cases and controls were also comparable on level of education. The predominant lung cancer cell type was adenocarcinoma. Despite matching on smoking status, cases were slightly more likely than controls to be current smokers and had higher smoking duration and intensity.

Whether analyzing all respondents or in-person interviews only, elevated effect estimates were noted for several types of PLD (Table 2). A relative risk estimate greater than two was shown for emphysema. Other elevated risks were noted for a history of chronic bronchitis, pneumonia, and for all PLDs combined. In general, analysis of only direct interviews did not alter relative risk patterns. For six categories of lung diseases (*e.g.* asthma, chronic bronchitis, pleurisy, pneumonia, tuberculosis, all PLDs), effect estimates showed further departure from the null when based only on direct interviews. For one category (emphysema), the effect estimate moved toward the null based on direct interviews.

Table 1. Characteristics of cases and controls, Missouri, 1994–1996

Characteristic	Cases (n = 676)	Controls (n = 700)
Mean age (years)	66.2 (SD* = 10.1)	66.4 (SD = 10.0)
Mean education level (years)	11.2 (SD = 2.7)	11.9 (SD = 11.9)
Interview type (%)		
Self	67.6	100
Surrogate	32.4	
Histologic type (%)		
Adenocarcinoma	32.7	
Squamous cell	17.6	
Large cell	1.9	
Bronchioalveolar	1.0	
Small cell	21.0	
Other	25.8	
Smoking history (%)		
Never	7.5	13.1
Former	26.2	28.8
Current	66.3	58.1
Mean smoking duration (years)	41.1 (SD = 12.0)	35.7 (SD = 14.4)
Mean smoking intensity (cigarettes/day)	25.3 (SD = 13.1)	18.6 (SD = 11.4)

* SD = standard deviation.

Table 2. Adjusted odds ratios[a] (ORs) and 95% confidence intervals (CIs) for the association between previous lung diseases and lung cancer among Missouri women, by interview type, 1992–1994

Previous lung disease	All subjects			Direct interviews only		
	No. cases /controls	OR	95% CI	No. cases /controls	OR	95% CI
None	234/336	1.0	–	151/336	1.0	–
Asthma	59/66	1.1	0.7–1.7	39/66	1.2	0.7–1.8
Chronic bronchitis	164/110	1.7	1.2–2.3	105/110	1.8	1.2–2.5
Emphysema	121/39	2.7	1.8–4.2	67/39	2.5	1.6–4.1
Pleurisy	91/104	1.1	0.8–1.5	66/104	1.2	0.8–1.8
Pneumonia	319/240	1.6	1.2–2.0	229/240	1.8	1.4–2.4
Tuberculosis	10/12	0.9	0.4–2.2	5/12	0.8	0.3–2.4
Any previous lung disease	442/359	1.5	1.2–1.9	306/359	1.6	1.3–2.1

[a] Adjusted for pack-years of smoking.

Because PLDs identified close to the time of cancer diagnosis could conceivably be misdiagnoses resulting from early lung cancer symptoms, we evaluated the effects on risk estimates of a "latency exclusion" of up to three years (based on the date of initial diagnosis of the PLD) (Table 3). When these exclusions were taken into account, ORs remained statistically significantly elevated only for emphysema. For the category of any PLD, ORs dropped by 27% with a 1-year latency exclusion.

We also calculated relative risk estimates by age group. The OR for any PLD for women less than age 65 years was 1.4 (95% CI = 1.0–2.1). The corresponding value for women aged 65–74 years was 1.4 (95% CI = 1.0–1.9). For the age group 75 years and older the OR was 2.0 (95% CI = 1.2–3.1).

The broader interval between diagnosis of PLD and lung cancer diagnosis was also used as a stratifying variable. For women who had any PLD diagnosed within the past 30 years the OR was 1.9 (95% CI = 1.4–2.5). For a PLD diagnosis of more than 30 years prior to lung cancer diagnosis the effect estimate was 0.9 (95% CI = 0.7–1.3).

Negligible differences were noted when lung cancer risk due to PLD was stratified by smoking category. For never smokers the risk due to any PLD was 1.8 (95% CI = 0.9–3.6). Among ever smokers (former and current), the OR was 1.7 (95% CI = 1.4–2.1).

Table 3. Adjusted odds ratios[a] (ORs) and 95% confidence intervals (CIs) for the association between previous lung diseases and lung cancer among Missouri women, by latency exclusion category, 1992–1994

Lung disease status	Latency exclusion							
	None		One year		Two years		Three years	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
None	1.0	–	1.0	–	1.0	–	1.0	–
Asthma	1.1	0.7–1.7	0.8	0.5–1.3	0.8	0.5–1.2	0.7	0.5–1.2
Chronic bronchitis	1.7	1.2–2.3	1.3	0.9–1.8	1.2	0.9–1.7	1.2	0.9–1.7
Emphysema	2.7	1.8–4.2	2.1	1.3–3.2	2.4	1.5–3.9	2.4	1.4–3.9
Pleurisy	1.1	0.8–1.5	0.9	0.6–1.2	0.8	0.6–1.2	0.8	0.6–1.2
Pneumonia	1.6	1.2–2.0	1.2	0.9–1.5	1.1	0.9–1.4	1.1	0.8–1.4
Tuberculosis	0.9	0.4–2.2	0.8	0.3–1.9	0.7	0.3–1.8	0.7	0.3–1.8
Any previous lung disease	1.5	1.2–1.9	1.1	0.9–1.4	1.0	0.8–1.3	1.0	0.8–1.3

[a] Adjusted for pack-years of smoking.

In analyses by histologic types, effect estimates were largest for squamous cell carcinoma. For example, the adjusted risk estimate for any PLD and lung cancer was 2.4 (95% CI = 1.5–3.8) for squamous cell carcinoma, 1.4 (95% CI = 1.0–2.0) for "other" cell types, 1.4 (95% CI = 1.0–1.9) for adenocarcinoma, and 1.4 (95% CI = 0.9–2.1) for small cell carcinoma.

Discussion

Our study builds on a small, but growing, body of literature suggesting that certain types of PLDs increase the risk of lung cancer in women. The relationships observed are generally robust when only in-person interviews are used in analyses. Our findings also indicate that taking account of the window of PLD diagnosis (*i.e.* a latency exclusion) may have a substantial effect on risk estimates. Earlier studies are inconsistent on the presence and magnitude of a latency exclusion. Our data can be interpreted in two ways. One might argue that, when a latency exclusion is taken into account, there is only weak evidence of a relationship between PLD and lung cancer. However, when earlier epidemiologic findings and underlying biological and genetic factors are considered (discussed later in this section), an association between PLD and lung cancer is plausible.

In a multi-center study in the United States, Wu *et al.* [8] found that history of any PLD resulted in elevated lung cancer risk (OR = 1.6; 95% CI = 1.2–2.0). Statistically significant increased risks for lung cancer were observed for prior history of asthma and chronic bronchitis. Borderline significance was shown for previous history of emphysema (OR = 2.6; 95% CI = 1.0–6.8). In addition, among younger cases (*i.e.* < 55 years) elevated risk was noted for pneumonia (OR = 2.9; 95% CI = 1.5–5.6) and tuberculosis (OR = 9.1; 95% CI = 1.6–49.7). These relationships observed were unchanged after adjustment for potential confounders such as environmental tobacco smoke (ETS) and dietary factors. Associations between PLD and lung cancer were based on lung diseases reported at least one year prior to cancer diagnosis.

Alavanja *et al.* [7] conducted a large case–control study in Missouri and found an elevated risk of adenocarcinoma associated with any PLD (OR = 1.4; 95% CI = 1.0–2.1). A three-year latency exclusion was used. Although effect estimates were not always statistically significant, each type of lung disease except for chronic bronchitis showed some elevation in risk. For some types of PLD, ORs changed considerably whether based on all subjects or only on in-person interviews (*i.e.* excluding proxy data). For example, risk due to any previous history of asthma increased sharply when analyses excluded proxy interviews.

In our study, the most consistently elevated lung cancer risk was associated with a history of emphysema, with effect estimates ranging from 2.1 to 2.7 depending on the presence of proxy interview and the latency exclusion. These data are consistent with at least two earlier studies [4, 8] showing larger effect estimates for emphysema than for other types of PLD.

There is growing biological and genetic evidence for a relationship between PLD and lung cancer. Due to lung damage from PLD, airway clearance mechanisms may be impaired and immune function compromised, leading to heightened susceptibility to lung carcinogens [8, 22, 23]. There is increasing interest in whether carriers of an alpha$_1$-antitrypsin deficiency (α_1AD) are at increased risk of lung cancer. It is already established that some PLDs, in particular chronic bronchitis and

emphysema, are associated with α_1AD [24, 25]. Yang *et al*. [26] recently demonstrated lung cancer patients are significantly more likely to carry the α_1AD allele. In addition, lung cancer diagnosis at a later age may be a modifying factor suggesting a later-stage effect of α_1AD. Another example of an underlying biological mechanism for PLD and lung cancer involves the finding of a positive association between *Chlamydia pneumoniae* infection and lung cancer [27]. *C. pneumoniae* is a known risk factor for PLDs such as chronic bronchitis and asthma [28, 29], and is also promoted by smoking [30]. It has been postulated that nitric oxide and other free radicals released by activated inflammatory cells have a role in stomach carcinogenesis [31]. Thus, *C. pneumoniae* may induce lung cancer through mediators of inflammation (*e.g*. free radicals) resulting from chronic infection [27]. It is also possible that PLD and lung cancer share a common "biological clock" (*i.e*. similar latency periods), which may in part mask the relationship between PLD and lung cancer. Prospective studies that collect biological tissue are needed to better understand the biological and genetic basis for PLD and lung cancer.

The major limitation of our study (and earlier reports) is our reliance on self-reported data. We did not attempt to validate PLD reports with individual medical records. However, in an earlier Missouri study that followed a similar protocol [7], test–retest reliability for PLD was high. A potential advantage of our study over other lung cancer studies among smokers is the ability to better control the effects of smoking on PLD-associated effect estimates via our combined strategy of matching and adjustment during analysis.

Although the biological mechanisms by which PLD influences lung cancer are not fully understood, their long-term effects may lead to heightened susceptibility to lung cancer from other carcinogens. In summary, our study suggests that certain types of PLD are associated with an increased risk of lung cancer in women. Therefore, it seems prudent that individuals with PLD take extra precautions to reduce exposures to other lung carcinogens such as active smoking, environmental tobacco smoke, and radon. A better understanding is needed of genetic susceptibility of both PLD and lung cancer, and how these factors may interact with modifiable risk factors.

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